## II. REMARKS

Claims 17-36 are pending. Claims 18 and 19 are amended. No new matter is added.

**Claim Objection**

Claims 34 and 35 are objected for reciting incorrect claim numbers. In response, Applicants renumber claims 35 and 36 as suggested by the Office.

**Rejections under 35 U.S.C. § 102**

Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walker et al. 1994 (Walker), Pirttila et al. 1994 (Pirttila), WO01/62801, or Naslund et al. 1994 (Naslund). Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Solomon et al. 1996 (Solomon). Claims 17-19, 22-23, 28 and 36 are rejected under 35 U.S.C. § 102(a) as alleged being anticipated by Huse et al. 2002 (Huse).

Applicants respectfully traverse. None of the cited references discloses each and every element of the claimed monoclonal antibody, which specifically binds to one or more epitopes present on the first 5 to 7 N-terminal amino acids of Aβ11-x polypeptide and does not specifically bind to a full length Aβ1-40/42 peptide.

It is well known in the art that various Aβ peptides are present in diseased and normal aging brains, including the N-terminal truncated Aβ11-x and the full-length Aβ1-40/1-42 (Aβ1-40/42). As Aß11-x peptides are the major species identified in the brains of patients with Alzheimer's disease (AD), it is important to specifically detect Aβ11-x without the cross-reactivity of Aβ1-40/42 for developing effective diagnosis and treatment for AD. See specification, page 2, lines 18-26, *"Recently, it was demonstrated that BACE-1 is the major ß-secretase required for cleavage of APP at position +1 and that overexpression of BACE-1 results in an additional cleavage at the +11 site of the Aß, generating shorter Aß11-40 and Aß11-42 fragments, hereinafter also referred to as the Aß11-x peptides. These Aß peptides have been detected in conditioned medium of primary rat neuronal cell cultures and mouse N2a cells, suggesting that they are normal APP cleavage products generated in neurons (3, 4, 5). Significantly, these shorter Aß*

*fragments have also been identified as major species in AD brains and normal aging brains by biochemical analysis as well as Down syndrome brains with AD pathology by immunohistochemistry studies."* and lines 30-35, *"Despite the progress which has been made in understanding the underlying mechanisms of AD and other Aβ-related diseases, there remains a need to develop methods and compositions for diagnosis and treatment of the disease(s). Thus, the ability to monitor cellular processing of the amyloid precursor protein would be of significant value in the diagnosis, prognosis, and therapeutic supervision of Alzheimer's disease."* Therefore, the present application provides the claimed antibody which (a) binds to one or more epitopes on the first 5-7 amino acids of Aβ11-x, (b) binds specifically to Aβ11-x, and (c) does not specifically bind to a full length Aβ1-40/42 peptide.

None of the prior art discloses a monoclonal antibody with all three of these characteristics. To illustrate the differences in the properties among the antibodies, Applicants submit the table below and discuss each antibody hereafter.

| | Epitope of Aβ | Binds to Aβ11-x | Binds to Aβ1-40/42 |
|---|---|---|---|
| Claimed antibodies | 11-15/17 (first 5-7 amino acids of Aβ11-x) | Yes | No |
| 10D5 (Walker) | 3-6 (as evidenced by Frenkel) | Unknown | Yes |
| 4G8 (Prittila, WO01/62891 and Huse) | 17-24 | Unknown | Yes |
| 266 (WO01/62801) | 17-25 | Unknown | Yes |
| 6E10 (Pirttila and Naslund) | 4-9 (as evidenced by product description) | Unknown | Yes |
| AMY-33 (Solomon) | 1-28 | Unknown | Yes |
| 6D/3D (Solomon) | 8-17 | Unknown | Yes |
| BAN50 (Huse) | 1-10 | Unknown | Yes |
| BNT77 (Huse) | 11-16 | Yes | Yes |
| BA27 (Huse) | Unknown | Unknown | Yes |
| BC05 (Huse) | Unknown | Unknown | Yes |

As can be easily seen with reference to the table, all of the previously disclosed antibodies differ from the claimed antibodies in at least one way. All of the art-disclosed antibodies specifically bind to full-length Aβ1-40 and/or 1-42, in contrast to the claimed

antibodies. Some of the antibodies of the prior art also differ from the claimed antibodies in other ways, as discussed in detail below.

Walker discloses that the monoclonal antibody 10D5 binds to Aβ1-16 and native Aβ. See page 377, right column, third paragraph, *"...we used monoclonal antibody (MAb) 10D5, a murine IgG, kappa light chain (whole IgG and/or Fab fragments) to amino acids 1-16 of Aβ."* and page 379, left column, fourth paragraph, *"β-amyloid in untreated, fresh-frozen tissue sections was robustly labeled by antibody 10D5, whereas normal (non-Aβ-immune) mouse IgG did not bind to native Aβ in this tissue (data not shown)."* The antibody 10D5 is also disclosed by Frenkel et al. 1998, J. Neuroimmunology 88: 85-90 (Frenkel); submitted previously. Frenkel states that 10D5 was obtained from Dr. D. Schenk, the senior author of Walker. See page 86, second paragraph, *"Monoclonal antibodies, 6C6 and 10D5, raised against soluble fragment of position 1-28 of βAP, were kindly provide by Dr. D. Schenk..."* Subsequent analysis in Frenkel indicates that 10D5 has a minimal epitope of Aβ3-6 and binds to Aβ1-40. See Frenkel, page 88, Abstract, *"The peptide EFRH inhibits binding of mAbs 6C6 or 10D5 to β-amyloid peptide in affinities identical to those obtained with the peptides corresponding to positions 1-9, 1-16 and 1-40 of [A]β-peptide. These findings confirm that the peptide EFRH which is located at positions 3-6 within β-amyloid peptide represents the sequential epitope of mAbs 6C6 and 10D5."* Accordingly, 10D5 binds to full-length Aβ1-40 at Aβ3-6. Further, 10D5 cannot not bind to Aβ11-x, since Aβ11-x does not contain the 10D5 binding epitope. Thus, 10D5, disclosed by Walker, differs from the claimed antibody in all three ways: the Aβ epitope to which it binds, its lack of specificity for Aβ11-x and its specificity for full length Aβ1-40.

Pirttila discloses the monoclonal antibodies 4G8 and 6E10. 4G8 is also disclosed in WO01/62801; 6E10 is also disclosed in Naslund. The properties of these antibodies are discussed below.

WO01/62801 discloses that monoclonal antibodies 266 and 4G8 bind to full-length Aβ1-40/42; see Example 15, *"Using this method, the affinity of mouse antibody 266 for both Aβ1-40 and for Aβ1-42 was found to be 4pM. The affinity of 4G8 for Aβ1-40 was 23nM and for Aβ1-42 was 24nM."* The binding epitope of 266 is identified to be Aβ17-25; see Example 16 of WO01/62801, *"the binding epitope for the mouse antibody*

*266 appears to be between amino acids 17 and 25 of Aβ."* Additionally, the binding epitope of 4G8 is identified as Aβ17-24 in Prittila; see page 91, right column, fourth paragraph, *"The monoclonal antibody (mAb) 4G8 was specific to an epitope present on 17-24 amino acids of the Aβ-peptide..."* Accordingly, 266 and 4G8 differ from the claimed antibody in at least two ways: the Aβ epitope to which they bind and the specificity for full length Aβ1-40/42.

Naslund and Pirttila both disclose the monoclonal antibody 6E10 binds to Aβ at amino acids 1-16. See Naslund, page 8379, left column, second paragraph, which discusses the SDS/PAGE immunoblot shown in Figure 2 of Naslund, and states that *"The membrane was . . . probed with monoclonal antibody 6E10 directed against residues 1-16 of Aβ."*; and Pirttila, page 91, right column, *"The monoclonal antibody (mAb)...6E10 was raised to a peptide corresponding to the first 16 amino acid residues of Aβ peptide."* Subsequent analysis indicates that the epitope of the 6E10 antibody is within Aβ4-9; see product prescription submitted previously. Naslund also discloses that this antibody binds to full-length Aβ1-40/42; see page 8380, Figure 2B, showing an SDS/PAGE analysis of crude hexafluoroisopropanol (HFIP) extract and purified monomeric Aβ1-40/42 with a molecular weight of 4 kDa which is identified by immunoblotting with 6E10. According to Naslund at page 8379, right column, first paragraph, *"[t]he indicated 4-kDa peptide (Fig. b) was identified as Aβ peptide by N-terminal microsequencing."* Thus, 6E10 differs from the claimed antibody in at least two ways: the Aβ epitope to which it binds (amino acids 4-9 vs. 11-15/17) and the specific binding to full length Aβ1-40/42.

Solomon discloses the monoclonal antibodies AMY-33 and 6F/3D, both of which bind to full-length Aβ1-40. See page 452, and right column, third paragraph, *"Synthetic βA4-(1-40) was obtained from Sigma...To determine the soluble βA4 the supernatants were then incubated for another 60 min with an excess of mAb AMY-33 and/or 6F/3D...to produce immunocomplexed βA4."* Thus, AMY-33 and 6F/3D differ from the claimed antibody in at least one way: specific binding to full-length Aβ1-40.

Huse discloses the monoclonal antibodies 4G8, BAN50, BNT77, BA27, and BC05. The differences between 4G8 and the claimed antibodies are discussed above. According to Huse, BAN50 recognizes Aβ1-10 and binds to Aβ1-40/42, BNT77

recognizes Aβ11-16 and binds to both Aβ1-40/42 and Aβ11-x, BA27 binds to Aβ1-40 and BC05 binds to Aβ1-42. See page 16279, left column, fourth paragraph *"mAbs BAN50 and BNT77, directed against amino acids 1-10 and 11-16 of Aβ, respectively, were used as capturing antibodies. End-specific, horseradish peroxidase-conjugated mAbs BA27 (for Aβ40) and BC05 (for Aβ42) were then used for detection."*; and page 16280, left column, first paragraph, *"BAN50 captures primary Aβ1-40 and Aβ1-42, whereas BNT77 detects N-terminally truncated species as well as full-length peptides."* Thus, the antibodies disclosed in Huse all differ from the claimed antibody in at least one way: the specificity for full-length Aβ peptides. Additionally, at least antibody 4G8 and BAN50 recognize a different epitope than the claimed antibodies.

Clearly, none of the antibodies in the cited documents have all three properties of the claimed antibody. Therefore, Walker, Pirttila, WO/0162801, Naslund, Solomon and Huse do not anticipate the monoclonal antibody recited in the claims.

With regard to the Office notion at page 6 that *"Applicant has provided no showing that the antibodies in the art have characteristics different from those specified by Applicant and do not in fact cross react with the full length of Aβ-40/42 in the same titration or at the same concentration as those of the prior art. Applicant fails to provide side-by-side comparisons to demonstrate that the claimed antibody is different from those antibodies disclosed by Walker et al., Pirtila, WO0162801, Naslund and Huse"*, Applicants respectfully traverse. It is not necessary for Applicants to submit side by side data showing the claimed antibodies differ from the prior art, since the prior art teaches that the claimed antibodies have at least one characteristic which differs from the antibodies of the claims: namely, specific binding to full length Aβ1-40 and/or Aβ1-42. As can be seen in Fig. 2A, 2B and 2C of the captioned application showing data for a specific antibody of the claims, the claimed antibody does not bind to full length Aβ1-40, even at concentrations as high as 1000 ng/ml; yet it binds to Aβ11-x at a concentration as low as 0.1 ng/ml. The prior art teaches that all antibodies described therein specifically bind to Aβ1-40/42. The Office has not presented any reasoning to doubt the veracity of the statements in the art that the disclosed antibodies bind to full-length Aβ1-40/42; nor any reasoning to doubt the data in the specification showing specific binding to Aβ11-x,

and no specific binding to Aβ1-40. Thus, the claimed antibodies do, in fact, differ from the antibodies disclosed in the prior art, despite their structural similarity as antibodies.

Further, Applicants submit that the claimed monoclonal antibody has been utilized to specifically recognize Aβ11-x polypeptide by a person skilled in the art of Alzheimer's disease. This is evidenced by Liu et al. published in Acta Neuropathology 112: 163-174, titled 'Characterization of Aβ11-40/42 peptide deposition in Alzheimer's disease and young Down syndrome brains: implication of N-terminally truncated Aβ species in the pathogenesis of Alzheimer's disease' submitted herein. In Liu et al., the monoclonal antibody M11 which corresponds to the claimed antibody is used to specifically detect the truncated Aβ11-40/42 peptide whereas the monoclonal antibodies 4G8, which is the antibody disclosed in Prittila, WO01/62891 and Huse is used to detect the full-length Aβ1-40/42 peptide. This is illustrated, for example, at page 165, left column, second paragraph states *"Antibodies: The following panel of antibodies was utilized to analyze different Aβ species...monoclonal antibody (mAb) M11 (a gift from Jonson & Johnson/Janssens Pharmaceutica) specifically recognizes free Aβ11-40/42; mAb M266 (a gift from Eli Lilly) and 4G8 recognize total Aβ (epitope 13-28 and 17-24 of Aβ11-x, respectively)"* and page 166, left column, second paragraph to right column, first paragraph states "Characterization of free *Aβ11-40/42 specific antibody M11 and pyro Aβ11-40/42 specific antibody P82....To demonstrate the specificity of M11 and P82 for free and pyro Aβ11-40/42, respectively, synthetic Aβ11-40 and pyro Aβ11-40 peptides were used in Western blot and ELISA analyses...Thus, P82 specifically binds to pyro Aβ11-40/42 peptides whereas M11 specifically recognizes free Aβ11-40/42 peptides".* Clearly, the skilled artisan recognizes the claimed antibody specifically recognize the truncated Aβ11-x peptides and not the full-length Aβ1-40/42 and utilized the claimed antibody to investigate the role of the Aβ species in the Alzheimer's disease. This clearly support that the claimed antibody has function, property and characteristics different from the art-disclosed antibody.

Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 102 are respectfully requested.

**Rejections under 35 U.S.C. § 103**

Claims 17-25, 28 and 31-36 are rejected to under 35 U.S.C. § 103(a) for being unpatentable over Huse in view of Walker and WO01/62801.

As discussed above, all of the antibodies disclosed in Huse lack one or more properties of the claimed antibodies. None of the art provides motivation to modify the antibodies of Huse to arrive at the claimed antibodies.

One of the antibodies disclosed in Huse, BNT77, was produced using the Aβ11-16 immunogen (including the epitope of the claims) and binds N-terminal truncated (Aβ11-x) peptides. However, in contrast to the claimed antibodies, BNT77 also binds to full-length (Aβ1-40/42) Aβ peptides. One of ordinary skill in the art, reading Huse, would not have been motivated to produce an antibody of the claims, since it flows from Huse that an antibody which could specifically bind to N-terminal truncated Aβ peptides at one or more epitopes in the first 5-7 N-terminal amino acids would also specifically bind to full-length Aβ1-40/42 peptides. In fact, Huse teaches away from producing the claimed antibody, since it teaches that an antibody produced with the first 5 N-terminal amino acids of Aβ11-x would bind to full-length Aβ1-40/42 peptides.

Both Walker and WO01/62801 are silent as to whether the antibodies disclosed therein specifically bind to Aβ11-x peptides. The antibodies of both Walker and WO01/62801 bind to full length Aβ1-40/42 peptides. Therefore, they do not cure the deficiency in Huse.

Accoridngly, the rejection is obviated. Reconsideration and withdrawal of the rejection under U.S.C. § 103 are respectfully requested.

**Rejections under 35 U.S.C. § 112**

Claims 18 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting "binds to human Aβ11-x" and "binds to human Aβ11-x", respectively.

In respone, Applicants amend claims 18 and 19 to recite "Aβ11-x polypeptide at one or more epitopes present on the first 5 to 7 N-terminal amino acids". Accordingly, the rejection is obviated. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph are respectfully requested.

**Allowable Subject Matter**

Applicants greatly appreciate the Office's indication that claims 26-27, 29 and 30 would be allowable if rewritten in independent form. As discussed above, Applicants believe that claims 17-36 are allowable and therefore request early consideration and prompt allowance of the pending claims. Should the office require anything further, it is invited to contact applicants' representative at the telephone number below.

Respectfully submitted,

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